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Provision and Availability of Genomic Medicine Services in Level IV Neonatal Intensive Care Units

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Ethics Declaration

This study was approved by the Boston Children's Hospital Institutional Review Board.
Completion of the study survey was taken to constitute informed consent to participate.

Conflict of Interest

The authors have no relevant conflicts of interest to disclose. Monica H Wojcik reports receiving compensation for consulting from Sanofi and Illumina and providing expert witness/consulting services in medical malpractice cases.

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Abstract

Purpose: To describe variation in genomic medicine services across level IV Neonatal Intensive Care Units (NICUs) in the United States (US) and Canada.

Methods: We developed and distributed a novel survey to the 43 level IV NICUs belonging to the Children's Hospitals Neonatal Consortium (CHNC), requesting a single response per site from a clinician with knowledge of the provision of genomic medicine services.

Results: Overall response rate was 74% (32/43). While chromosomal microarray and exome or genome sequencing (ES or GS) were universally available, access was restricted for 22% (7/32) and 81% (26/32) of centers, respectively. The most common restriction on ES or GS was requiring approval by a specialist (41%, 13/32). Rapid ES/GS was available in 69% of NICUs (22/32). Availability of same-day genetics consultative services was limited (41%, 13/32 sites), and pre- and post-test counseling practices varied widely.

Conclusions: We observed large inter-center variation in genomic medicine services across level IV NICUs: most notably, access to rapid, comprehensive genetic testing in timeframes relevant to critical care decision-making was limited at many level IV CHNC NICUs, despite a significant burden of genetic disease. Further efforts are needed to improve access to neonatal genomic medicine services.

Keywords

neonate; infant; intensive care unit; genetic; genomic; exome sequencing; genome sequencing

Introduction

Many genetic conditions manifest in the perinatal period, from congenital anomaly syndromes suspected via prenatal imaging to postnatal clinical manifestations such as seizures or metabolic derangements. Neonates with such conditions often present to level IV neonatal intensive care unit (NICUs). These NICUs support pediatric subspecialty medical and surgical services for at-risk infants and serve as referral hospitals for infants in their region.[1] Infants in level IV NICUs therefore comprise a population with complex care needs, enriched for genetic conditions, with high risk of morbidity, mortality, and with high costs of care.[2–4] Identification of an accurate and precise genetic diagnosis for these infants may aid in timely clinical decision-making and improve clinical outcomes.[5,6] Rapid genomic sequencing - exome sequencing (ES) or genome sequencing (GS) with results available

in a matter of days - has been shown in multiple studies to have high diagnostic and clinical utility in the NICU[5–8] that may lead to cost savings. However, despite the burden of genetic disorders in level IV NICUs and the proven clinical utility of these diagnoses, implementation of genomic medicine services in the NICU remains highly variable,[9–11] with commonly-cited barriers including cost and clinical genetics workforce limitations.[12,13]

The Children's Hospitals Neonatal Consortium (CHNC) is a network of 46 level IV NICUs in North America. Prior research by the CHNC has documented wide variation in practice and availability of services in multiple clinical areas.[14,15] Variation in genomic medicine services has not been previously described among CHNC sites. Therefore, we sought to determine the availability of such services, including personnel and testing resources, scope of practice, and barriers to genomic medicine implementation in level IV NICUs participating in the CHNC.

Methods

Survey Development

Survey items were informed by prior research in this area[9,11,13] and were validated by cognitive interviewing with key stakeholders in the provision of genomic medicine services such as genetic counselors, neonatologists, and geneticists. Survey items underwent iterative revision by all members of the research team.

Survey Administration

The CHNC email contact list was used to identify potential respondents from each of the 43 NICUs comprising the CHNC (at the time of distribution) who would be aware of clinical genetics services at their institution. Participants were invited to complete this survey electronically via REDCap[16], with results collected anonymously and completion of the survey taken to constitute informed consent to participate in the study. This study was approved by the Boston Children's Hospital Institutional Review Board.

Analysis

We utilized standard approaches for descriptive statistics. Comparison of continuous variables was performed using a Mann-Whitney U test for non-normally-distributed variables and comparison of categorical variables was performed using Fisher's exact test. Data analysis was performed using RStudio.[17]

Results

Characteristics of Respondents

Responses were received from 32 of 43 CHNC sites, for a response rate of 74%. Respondents were primarily neonatologists (59%, 19/32) or geneticists/genetic counselors (28%, 9/32), some of whom were medical directors (16%, 5/32), or division or section chiefs (19%, 6/32). More than half (59%, 19/32) were members of the CHNC genomics focus group. Respondents were highly experienced clinicians with a median of 20 years since the respondent's highest degree (interquartile range, IQR, 10–28).

Access to Genetic Testing

Nearly all types of genetic testing included in the survey were available at responding NICUs (Table), with restrictions in place for all tests: particularly for ES or GS, where less than 20% of NICUs reported unrestricted access. Rapid testing, with results available within 2 weeks, was possible at 91% of NICUs (29/32), mostly related to chromosomal analysis; 69% of NICUs (22/32) reported availability of either rapid ES or GS, and a large majority did not have rapid turnaround time for single gene tests, gene panels, and mitochondrial sequencing (Table 1). Half of responding NICUs (16/32) have guidelines or decision support tools used to select infants for ES or GS. These guidelines were either related to eligibility for rapid ES/GS studies, or define criteria for clinical testing based upon phenotype and predicted ability to impact clinical management. Postmortem testing is available in 38% of NICUs (12/32), although an additional 44% (14/32) reported that this access to such testing is complicated, adjudicated on a case-by-case basis, and may require enrollment in research or payment out-of-pocket. Of the 12 NICUs do offer postmortem testing, available tests included karyotype 10/12 (83%), chromosomal microarray (10/12, 83%), single gene or gene panel testing (9/12, 75%), and exome sequencing (10/12, 83%). Reported barriers to postmortem testing include payment (14/32, 44%), lack of parental consent (8/32, 25%), ability to save samples for future testing (4/32, 13%), and lack of institutional support (4/32, 13%).

Approval processes for genetic testing varied widely by test, with the most common mechanism across all tests involving review by a non-neonatologist specialist (Figure 1A), although types of specialists varied (1B), as did the need for insurance approval (1C). For the 11 NICUs where insurance approval is sometimes or always required, tests needing insurance approval prior to ordering included CMA (2/11, 18%), single gene or gene panel testing (5/11, 45%), rapid or non-rapid ES/GS (9/11, 82%).

When asked to identify the major barriers to genetic testing in the NICU (selecting from a list provided, multiple selections allowed), the most common barrier identified was a requirement for parental samples for testing (15/32, 47%), followed by the pre-test counseling and consent process (13/32, 41%), insurance approval (12/32, 38%) and educational deficiencies (12/32, 38%), a requirement for specialist consult prior to test ordering (9/32, 28%), obtaining samples for testing (8/32, 25%) review committees (6/32, 18%), institutional approval processes (5/32, 16%), and lack of access to genetic counselors or geneticists (4/32, 13%).

Access to Clinical Genetics Consult Services

While all responding NICUs have specialists in genetics available for consultation, recommendations of the genetics consult services are returned within the same working day for 13/32 NICUs (41%), within 24 hours for 12/32 NICUs (38%), and later than 24 hours for 7/32 NICUs (22%). The point of contact for genetics consultations varied from a medical geneticist (22/32, 69%), genetic counselor (2/32, 6%), or either (8/32, 25%). Clinical genetics expertise in the form of a dual board (Medical Genetics and Genomics and Neonatal-Perinatal Medicine) certified physician or a neonatologist with “significant expertise” in clinical genetics was available in only 34% (11/32) of sites, and only 9% (3/32)

of the sites identified a medical geneticist focused on NICU consultation. Clinical genetics consultation prior to genetic testing was increasingly common with higher test complexity 3% (1/32) for karyotype, 6/32 (19%) for chromosomal microarray, 13/32 (41%) for single gene or gene panel testing, 24/32 (75%) for ES, 26/32 (81%) for GS, and 27/32 (84%) for mitochondrial sequencing ($p < 0.001$). For circumstances in which genetics consultations are not obtained, 13/32 (40%) of NICUs responded that pre-test counseling is simply not provided for karyotype or chromosomal microarray, and 8/25 (32%) reported that no pre-test counseling would be provided for single gene or gene panel testing. Neonatologists were reported to provide the pre-test counseling for karyotypes in 17/32 NICUs (53%), chromosomal microarrays in 14/32 (44%), single gene or gene panel testing in 11/32 (34%), and 5/32 (16%) for ES, GS or mitochondrial sequencing. For post-test counseling, nearly all sites (91%, 30/32) reported involving a geneticist or genetic counselor in all or nearly all cases.

Discussion

Our NICU-level comparison of availability and provision of genomic medicine services highlights concerning variation in practice. Notably, while rapid ES or GS have proven high diagnostic and clinical utility in the NICU setting, particularly in level IV NICUs,[5] we found that nearly one third of level IV CHNC NICUs – representing the highest level of NICU care in the United States and Canada – do not have access to either rapid ES or GS. Furthermore, access to ES/GS, whether rapid or not, was restricted in nearly all centers: most often requiring review by a specialist (who may be neither a medical geneticist nor a neonatologist) prior to ordering. At the same time, other types of testing that may be used to identify monogenic disorders if ES/GS is not available, such as single gene or gene panel testing, were rarely available on a rapid basis. Although rapid ES/GS is generally more costly than a single, less comprehensive test, the ability to obtain a result within days to weeks, while the infant is still in the NICU, greatly increase the clinical utility. Furthermore, because the alternative to early rapid ES/GS is often not just a single genetic test, but rather a diagnostic odyssey composed of a series of genetic tests that will not return within clinically meaningful timeframes, this alternative is less cost effective and of lower utility to clinicians, patients, and families.[2,7]

We also identified several process barriers related to genetic testing in the CHNC NICUs, where requirement for parental samples for trio ES/GS was identified as the most common barrier to sending genetic tests, followed by the pre-test counseling and consent processes. Although the need for approval processes and review by oversight committees was highly prevalent in these NICUs, these were not the most commonly cited barriers to access. This reflects the complexity of the current ES/GS ordering process in NICUs and the need for dedicated clinical champions or other mechanisms to support this workflow,[13,18] particularly when ES/GS is not being performed under a research study that provides staff to facilitate the process.[19] Although insurance approval was only reported to be a barrier in about one third of NICUs, the impact of payor policies on access to testing is difficult to quantify. These policies dictate reimbursement rates for genetic testing, which inform decisions made by approval or oversight committees, including whether testing is offered in the NICU at all.

In most centers, medical geneticists served in some way as gatekeepers for testing, especially ES/GS, via policies requiring genetics consultations prior to test ordering or by making geneticists a part of an approval process. Genetic testing may generate results beyond medical diagnoses, such as consanguinity or non-paternity, both of which may impact parental safety and family dynamics. It is therefore important that adequate pre-test counseling is provided, highlighting the benefits, limitations, and possible outcomes. The lack of any pre-test counseling for non-ES/GS testing in 30–40% of responding NICUs in our study is therefore concerning. Our finding that genetics consultations may not be available for same-day consultations in 69% of NICUs surveyed suggests that improving availability of medical genetics professionals in level IV NICUs may be one way to support responsible delivery of ES/GS. However, given workforce limitations within clinical genetics,[20] empowering neonatologists with basic genetic counseling skills also holds promise towards expanding access to genetic diagnosis for critically ill infants.[12]

Limitations of this study include the sample size and potential that the responding NICUs are not representative of the broader population of level IV NICUs in North America, though this is unlikely due to the breadth of the CHNC consortium. There is also the possibility that survey respondents were not aware of actual genetic testing practices in their NICUs, although the median of 20 years since highest degree for respondents suggests considerable clinical experience. Several respondents were geneticists, who are knowledgeable about genomic medicine services, and many of the responding neonatologists are members of the CHNC genomics focus group, reflective of more interest in and awareness of current genomic medicine practices; we acknowledge that NICUs with higher provision of genetics services may have been more likely to respond to our survey request. As practices are changing quickly over time, these results also represent a cross-sectional measure and cannot represent how hospitals may be modifying and/or improving their provision of genomic medicine services.

Overall, our results highlight significant variability in the provision of genomic services to a well-established, high-risk population. The need for further guidance and standardization regarding optimal implementation of genomic medicine in the NICU, particularly those serving complex populations such as the level IV NICUs cannot be overstated. Guidelines to direct use of ES/GS are reportedly present in half of these NICUs, though their content and utilization varied widely. The pairing of evidence-based guidelines for the identification of NICU patients requiring a genetic evaluation and optimal testing methodologies with well-established implementation science techniques will be crucial to better precision care for critically ill newborns.

Data Availability

De-identified survey data are available upon request, contingent upon a data transfer agreement.

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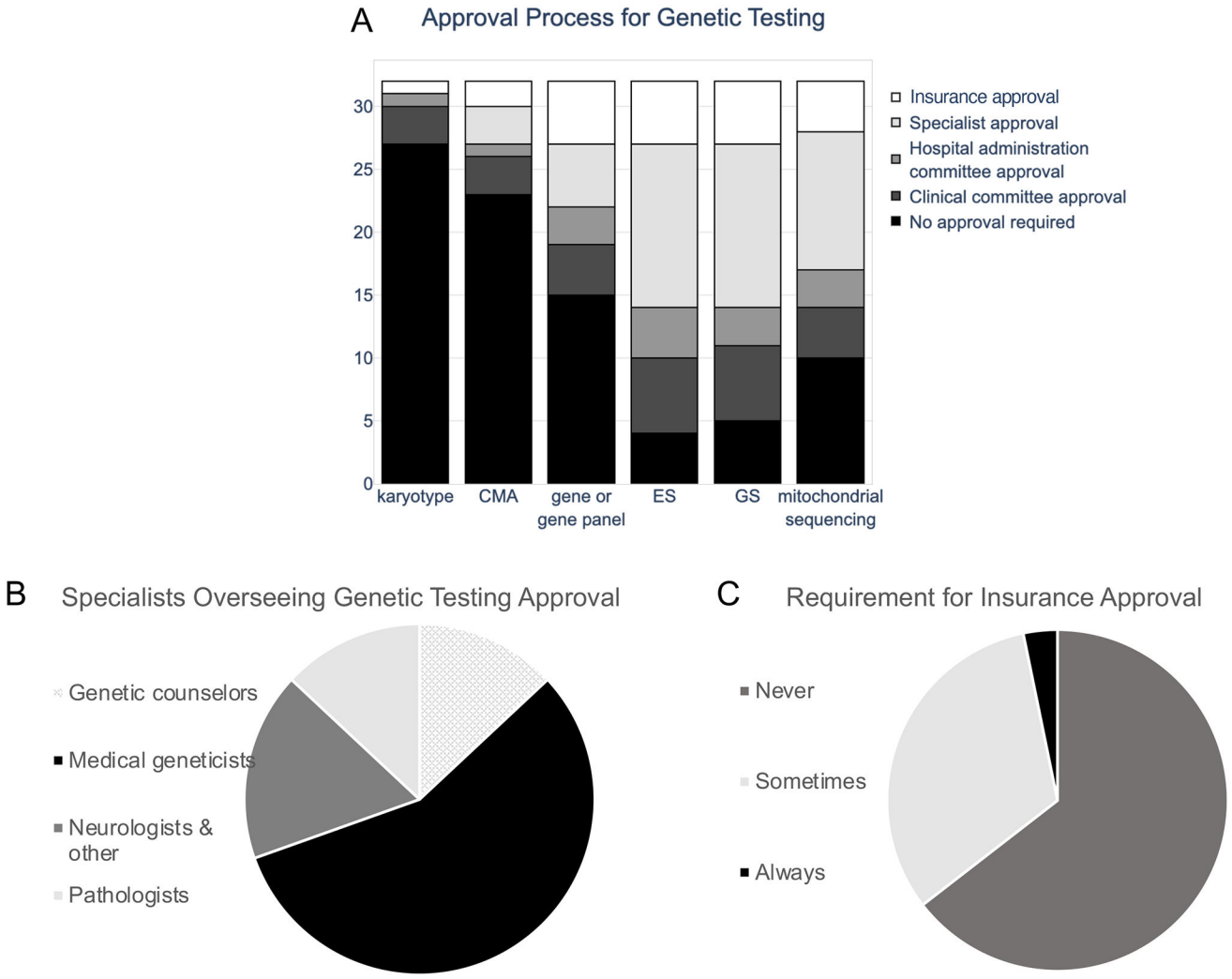

Figure 1: Variation in approval for genetic testing across level IV NICUs.

Variation in approval processes (A), types of specialists providing approval for testing (B), and insurance processes (C) is displayed. CMA, chromosomal microarray; ES, exome sequencing; GS, genome sequencing.

Table.

Genetic testing availability at level IV NICUs

Test type	Available without restriction (N, %)	Available with restrictions (N, %)	Results available within 2 weeks (N, %)
Karyotype	30, 94%	2, 6%	27, 84%
Chromosomal microarray	25, 78%	7, 22%	18, 56%
Single gene or gene panel	18, 56%	13, 41%	6, 32%
Exome sequencing	6, 19%	26, 81%	16, 50%
Genome sequencing[a]	5, 16%	24, 75%	18, 56%
Mitochondrial sequencing[a]	10, 32%	18, 56%	3, 9%

[a]Mitochondrial sequencing was reported to be unavailable at one institution, and GS and mitochondrial sequencing were each reported to be only available for research purposes at one institution. Two responses were missing for GS and mitochondrial sequencing.